Remarks

The Office action mailed July 29, 2005, has been carefully reviewed and considered. Claims 44, 45, 56, 92, 96 and 97 have now been cancelled. Claims 1, 2, 4, 10, 13, 16, 40, 54, 62, 90, 91 and 98 are currently amended. New claims 104-110 have been added. After entry of this Amendment, claims 1-19, 40-43, 54, 55, 59-63, 80, 81, 83-91, 93-95, and 98-110 should be pending.

I. Claim Objection

Claim 92 was objected to because it is a duplicate of claim 91. Claim 92 has been cancelled.

II. Claim Rejections - 35 U.S.C. § 102

Claims 1, 2, 8, 9, 13, 16-18, 40, 43-45, 56, 83, 84, 86-89 and 91-103 were rejected under 35 U.S.C. § 102 as allegedly being anticipated by A. Oplatka, "Breakthroughs and Views: Are Rotors at the Heart of All Biological Motors?" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, Volume 246, Pages 301-306 (1998) (Oplatka) with additional support from Merriam-Webster Online Dictionary, Definition of "array." Applicants respectfully traverse this rejection.

Independent claim 1

Independent claim 1 now clarifies that the first motor molecule is disposed upon a first surface, and the second motor molecule is unidirectionally aligned and disposed upon a second surface. The first and second arrays are arranged such that the second surface rotates relative to the first surface in a rotational direction that substantially parallels the unidirectional alignment of the second motor molecule. Examples of such geometry are shown, for instance, in FIGS. 1, 2, 3A, 3B, 5E, 6, 7A, 10, 11, 13, 14 and 15 of the present specification.

In the embodiment of FIG. 1 a layer 30 of a motor molecule (e.g, actin or a microtubule) is directionally disposed in the direction of arrows 32 on the outer surface of cylinder 12. The cylinder 12 rotates in a rotational direction 22 that substantially parallels the direction of arrows 32. In the embodiment of FIG. 2 a layer 130 of a motor molecule is directionally disposed in the direction of

arrows on the surface of cylinder 112. The cylinder 112 rotates in a rotational direction 122 that substantially parallels the direction of the arrows depicting the directionally aligned motor molecules. The embodiment of FIG. 6 is provided with layers 276a and 276b or directionally aligned motor molecules. Intermediate cylinder 272 and inner cylinder 270 rotate in the direction of arrow 280 which substantially parallels the direction of directionally aligned motor molecules.

The systems contemplated in Oplatka differ sharply in at least two aspects. Oplatka does not describe any system in which a first motor molecule is disposed on a first surface and a second motor molecule is disposed on a second surface. The Office action cites to page 302, col. 2, third paragraph of Oplatka as describing arrays of actin and myosin being disposed on a fixed surface. However, this passage from Oplatka describes a study in which actin filaments moved over myosin molecules fixed on a glass surface. The actin filaments and the myosin molecules were both disposed on the same surface rather than on different surfaces as recited in claim 1.

Moreover, the motor molecule rotation disclosed in Oplatka contrasts from the rotation recited in claim 1 due to the distinct differences between the structure of the motor recited in claim 1 and the systems mentioned in Oplatka. In all of the systems disclosed in Oplatka, the axis of rotation of the motor molecules is parallel to the longitudinal axis of the elongated motor molecules themselves. For example, at page 302, column 2, third paragraph, Oplatka describes an experiment involving "*axial* rotation of actin filaments sliding over myosin molecules fixed on a glass surface" (emphasis added). Oplatka also reports that another author proposed that "the actin helices rotate *about their axis* as the thick (myosin) and the thin (actin) filaments interdigitate" (page 301, column 1, first paragraph) (emphasis added). Oplatka also notes in the abstract that "[m]icrotubules also have been reported to rotate upon interacting with kinesin and dynein." Thus, it is individual motor molecules that rotate, not surfaces upon which they are disposed as recited in claim 1.

Moreover, there is no disclosure in Oplatka of a system wherein a second surface rotates relative to a first surface in a rotational direction that substantially parallels the directional alignment of a motor molecule as recited in new dependent claim 104.

Furthermore, there is no disclosure in Oplatka of a system in which there is a cylinder, shaft or cone having a longitudinal axis (which is also the axis of rotation for the cylinder, shaft or cone), and a second motor molecule is directionally aligned substantially perpendicular to the longitudinal axis as

recited in new dependent claims 108 and 110. In contrast, the axis of rotation described by Oplatka is parallel to the directional alignment of the actin filaments. On other words, the geometry disclosed in Oplatka would not work as a motor as claimed in claims 108 and 110.

Independent claim 16

The Examiner alleges that the Z-discs disclosed in Oplatka represent a driven member "wheel" as recited in claim 16. Claim 16 has been amended to recite "a rotatable wheel." There is no teaching in Oplatka that Z-discs rotate. Nor could there be such a teaching since rotation of the Z-discs would twist the entire sarcomere.

Independent claim 83

Claim 83 recites a motor that includes a first array of a first motor molecule disposed on a surface of a cylinder, shaft or cone. The Office action states that actin connected to Z-discs in muscles qualifies as an array of motor molecules disposed on the surface of a cylinder. However, the motor of claim 83 also includes a second array of a second motor molecule disposed on a second surface. In muscles, the second motor molecule (i.e., myosin) is not disposed on a surface. Rather, myosin is held in place by slender cross-connections between the myosin filaments (see, e.g., Ganong, Review of Medical Physiology, 10th ed. (1981), pp. 43-47 (attached as Exhibit A)).

III. Claim Rejections - 35 U.S.C. § 103

Claims 10, 41, 42, 54 and 55 were rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Oplatka in view of U.S. Patent No. 5,499,547 (Nagai) with additional support from Merriam-Webster Online Dictionary, Definition of "array." Applicants respectfully traverse this rejection.

Independent claim 54 recites two arrays of motor molecules disposed on two separate surfaces and interaction between these arrays and surfaces. As discussed above in connection with the rejection of claim 1 under 35 U.S.C. §102, Oplatka does not describe any system in which a first motor

molecule is disposed on a first surface and a second motor molecule is disposed on a second surface. Oplatka also does not disclose *rotating* a first surface relative to a second surface wherein both the first and second surfaces have motor molecules disposed thereon as now recited in claim 54. In contrast, Oplatka refers to the axial rotation of a motor molecule itself rather than any rotation of any surface upon which the motor molecule is disclosed.

The devices shown in Nagai et al. do not compensate for the lack in Oplatka of the rotation recited in claim 54. FIG. 13 of Nagai shows a pair of opposing surfaces -- one made up of a movable member 318 and the other made up of a fixing member 321, and a functional membrane 320a. Fig. 13 of Nagai also shows myosin 314 and actin 316 extending between these surfaces of 318 and 321. However, movable member 318 moves linearly relative to fixing member 321. There is no teaching in Nagai et al. that movable member 318 could move rotationally relative to fixing member 321. In other words, the device of FIG. 13 in Nagai et al. is a linear device rather than a rotary device.

Nagai et al. fails to provide any instructions as to how the device of FIG. 13 could be used in the structures shown in FIGS. 9-11 which are said at column 6, lines 50-59, to include "cylindrical surfaces, disc shapes and disc surfaces" and of "rotational motion." Thus, the mere mention of rotary motion in Nagai et al. is simply too vague to have enabled one to construct a motor as recited in claim 54.

Claim 54 also recites "at least one perforation in the first or second surface to allow permeation of a liquid fuel source through the surface to the motor molecules." Nagai is relied upon in the Office action for supplying the perforations that are missing from the disclosure in Oplatka. In particular, the Office action notes that Nagai "describes the myosin and actin forms [sic] a striated muscle" at column 7, lines 41-45 and that "muscle cells are cells which are known to comprise perforations." Nagai does not disclose the use of muscle **cells** as they exist in nature in any of the devices disclosed in Nagai. Thus, the disclosure in Nagai at column 7, lines 41-45, presumably was cited in the Office action as evidence of the existence of perforations in naturally-occurring muscle systems.

First, the fact that muscle is striated is not indicative that perforations exist as recited in claim 54. As noted on page 44, first column, fifth paragraph of Ganong (Exhibit A), "[t]he cross-striations characteristic of skeletal muscle are due to differences in the refractive indexes of the various parts of the muscle fiber." Hence, striations in muscle cells cannot be equated to perforations in muscle cells.

Furthermore, whether or not muscle **cells** include perforations is not relevant to the invention as claimed in claim 54. The motor of claim 54 includes at least one perforation in a surface upon which a motor molecule is disposed. In addition, the surfaces of claim 54 must move relative to each other due to the interaction of arrays of motor molecules. In naturally occurring muscle cells actin molecules and myosin molecules are not disposed on the surface of the cell membrane. Rather, actin filaments are attached to Z-discs and myosin filaments are attached to each other via cross-filaments. The construct of the interdigitated actin filaments and myosin filaments is surrounded by the sarcoplasmic reticulum (see Ganong, page 43, Figure 3-1, Exhibit A). There is no indication in either Oplatka or Nagai that Z-discs or the cross-filaments include perforations to allow permeation of a liquid fuel source.

Claims 10, 41 and 42 depend from claim 1. As discussed above, Nagai fails to disclose rotation of one surface relative to another surface as recited in claim 1. Therefore, Nagai does not overcome the deficiencies of Oplatka discussed in Section II above.

In summary, the combination of Oplatka and Nagai fails to disclose all of the elements of claims 10, 41, 42, 54 and 55. Furthermore, there would have been no suggestion or motivation for a person of ordinary skill in the art to have combined these references. Oplatka generally discloses experiments related to axial rotation of individual motor proteins in biological organisms. Nagai generally discloses a linear actuator including biological elements. No portion of Nagai can be combined with Oplatka to produce a functional molecular motor.

IV. Claim Rejections - 35 U.S.C. § 101

Claims 1, 2, 8, 9, 13, 40, 41, 43-45, 56 and 91-103 were rejected under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter. The Examiner alleges that Oplatka and Thomas et al. both disclose rotary molecular motors found in nature upon which claim 1 reads. Applicants respectfully traverse this rejection.

The examiner cites to the statement in the Oplatka abstract that "[a]xial protein rotation thus appears to be a common fundamental characteristic of actin- and of microtubule-based motility systems." However, as discussed above in connection with the 35 U.S.C. § 102 rejection, Oplatka does not disclose any system (human-made or naturally occurring) in which a first motor molecule is

disposed on a first surface and a second motor molecule is disposed on a second surface as now recited in claim 1. Moreover, Oplatka describes rotation of individual motor molecules rather than rotation of a surface upon which they are disposed as recited in claim 1.

The molecular motor depicted in Fig. 4(a) of Thomas et al. illustrates the transport of a vesicle along a microtubule inside a cell, wherein kinesin motor protein molecules attached to the vesicle pull it along the microtubule. There is no suggestion in Thomas et al. that the microtubule is disposed on a surface wherein that surface (not the microtubule molecule itself) rotates relative to the surface of the vesicle.

V. Conclusion

It is respectfully submitted that the present claims are in condition for allowance. Should there be any questions regarding this application, Examiner Smith is invited to contact the undersigned attorney at the telephone number shown below.

Respectfully submitted,

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EXHIBIT A

Excitable Tissue: Muscle | 3

Muscle cells, like neurons, can be excited chemically, electrically, and mechanically to produce an action potential that is transmitted along their cell membrane. They contain contractile proteins and, unlike neurons, they have a contractile mechanism that is activated by the action potential.

Muscle is generally divided into 3 types, **skeletal, cardiac,** and **smooth,** although smooth muscle is not a homogeneous single category. Skeletal muscle comprises the great mass of the somatic musculature. It has well-developed cross-striations, does not normally contract in the absence of nervous stimulation, lacks anatomic and functional connections between individual muscle fibers, and is generally under voluntary control. Cardiac muscle also has cross-striations, but it is functionally syncytial in character and contracts rhythmically in the absence of external innervation owing to the presence in the myocardium of pacemaker cells that discharge spontaneously. Smooth muscle lacks cross-striations. The type found in most hollow

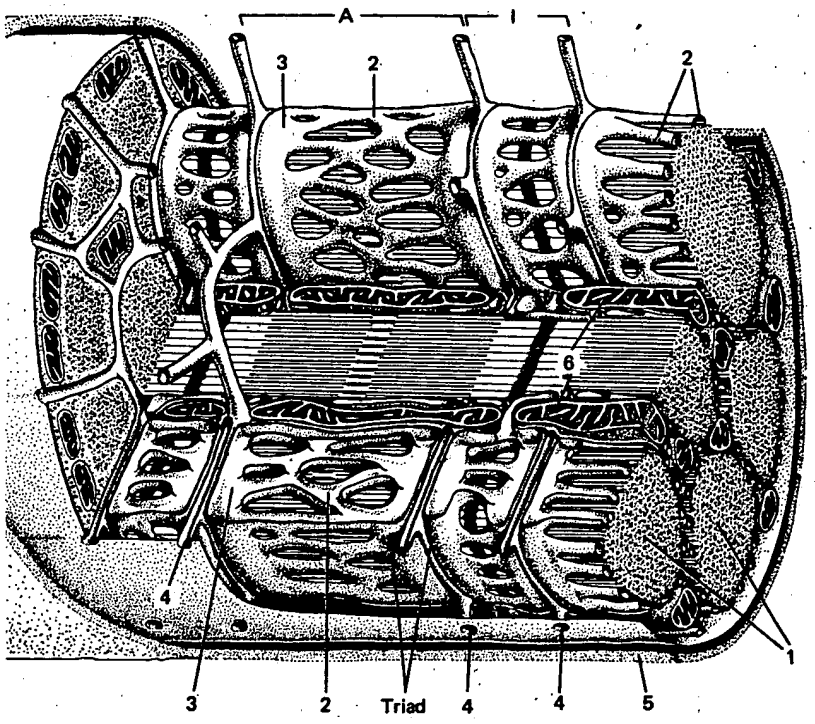


Figure 3–1. Mammalian skeletal muscle. A single muscle fiber surrounded by its sarcolemma has been cut away to show individual myofibrils (1). The cut surface of the myofibrils shows the arrays of thick and thin filaments. The sarcoplasmic reticulum (2) with its cisterns (3) surrounds each myofibril. The T system of tubules (4), which invaginates from the sarcolemma, contacts the myofibrils between the A and I bands, twice in every sarcomere. The T system and the adjacent cisterns of the sarcoplasmic reticulum constitute a triad. A basal lamina (5) surrounds the sarcolemma. (6), Mitochondria. (Modified and reproduced, with permission, from Krstić RV: *Ultrastructure of the Mammalian Cell.* Springer-Verlag, 1979.)

viscera is functionally syncytial in character and contains pacemakers that discharge irregularly. The type found in the eye and in some other locations is not spontaneously active and resembles skeletal muscle. There are contractile proteins similar to those in muscle in many other cells, and it appears that these proteins are responsible for cell motility, mitosis, and the movement of various components within cells (see Chapter 1).

SKELETAL MUSCLE

MORPHOLOGY

Organization

Skeletal muscle is made up of individual muscle fibers that are the "building blocks" of the muscular system in the same sense that the neurons are the building blocks of the nervous system. Most skeletal muscles begin and end in tendons, and the muscle fibers are arranged in parallel between the tendinous ends, so that the force of contraction of the units is additive. Each muscle fiber is a single cell, multinucleated, long, and cylindric in shape. There are no syncytial bridges between cells.

The muscle fibers are made up of fibrils, as shown in Fig 3–1, and the fibrils are divisible into individual filaments. The filaments are made up of the contractile proteins.

Muscle contains the proteins **myosin** (molecular weight 460,000), **actin** (molecular weight 43,000), **tropomyosin** (molecular weight 70,000), and **troponin.** Troponin is made up of 3 subunits, **troponin I, troponin T,** and **troponin C.** The 3 subunits have molecular weights ranging from 18,000 to 35,000.

Striations

The cross-striations characteristic of skeletal muscle are due to differences in the refractive indexes of the various parts of the muscle fiber. The parts of the cross-striations are identified by letters (Fig 3–2). The light I band is divided by the dark Z line, and the dark A band has the lighter H band in its center. A transverse M line is seen in the middle of the H band, and this line plus the narrow light areas on either side of it are sometimes called the pseudo-H zone. The area between 2 adjacent Z lines is called a **sarcomere.** The arrangement of thick and thin filaments that is responsible for the striations is diagrammed in Fig 3–3. The thick filaments, which are about twice the diameter of the thin filaments, are made up of myosin; the thin filaments are made up of actin, tropomyosin, and troponin. The thick filaments are lined up to form the A bands, whereas the array of thin filaments forms the less dense I bands. The lighter H bands in the center of the A bands are the regions where, when the muscle is relaxed, the thin filaments do not overlap the thick filaments. The Z lines transect the fibrils and connect

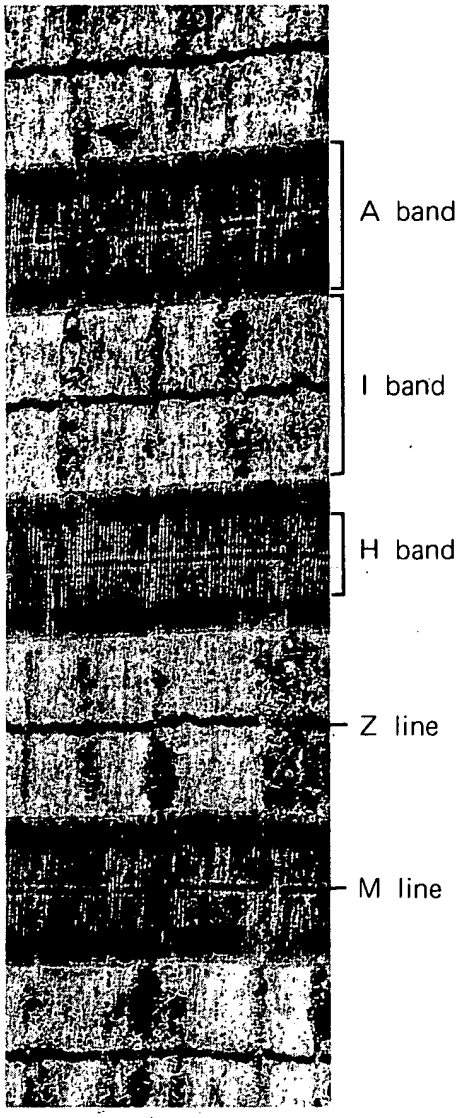


Figure 3–2. Electron micrograph of human gastrocnemius muscle. The various bands and lines are identified on the right. (× 13,500.) (Courtesy of SM Walker and GR Schrodt.)

to the thin filaments. If a transverse section through the A band is examined under the electron microscope, each thick filament is found to be surrounded by 6 thin filaments in a regular hexagonal pattern.

The myosin molecules in muscle are asymmetric, with the C-terminal portions forming enlarged globular heads. The heads contain an actin-binding site and a catalytic site that hydrolyzes ATP (see below). The molecules are arranged as shown in Fig 3–3, and cross-linkages form between the heads of the myosin molecules and the actin molecules. The myosin molecules are arranged symmetrically on either side of the center of the sarcomere, and it is this arrangement that creates the light areas in the pseudo-H zone. The M line is due to a central bulge in each of the thick

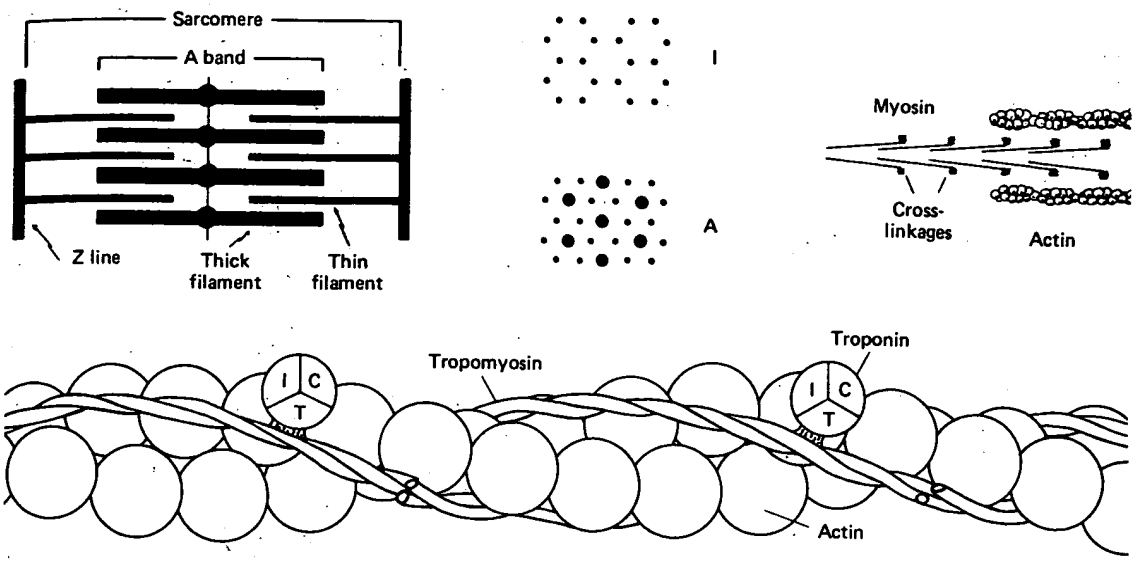


Figure 3–3. ***Top left:*** Arrangement of thin (actin) and thick (myosin) filaments in skeletal muscle. I and A represent a cross section through the I band and the lateral portion of the A band, respectively. ***Top right:*** Detail of structure of myosin and actin. ***Bottom:*** Diagrammatic representation of the arrangement of actin, tropomyosin, and the 3 subunits of troponin (I, C, and T; see text).

filaments. At these points, there are slender cross-connections that hold the thick filaments in proper array. There are several hundred myosin molecules in each thick segment.

The thin filaments are made up of 2 chains of globular units that form a long double helix. Tropomyosin molecules are long filaments located in the groove between the 2 chains in the actin (Fig 3–3). Each thin filament contains 300–400 actin molecules and 40–60 tropomyosin molecules. Troponin molecules are small globular units located at intervals along the tropomyosin molecules. Troponin T binds the other troponin components to tropomyosin, troponin I inhibits the interaction of myosin with actin (see below), and troponin C contains the binding sites for the Ca^{2+} that initiates contraction.

Sarcotubular System

The muscle fibrils are surrounded by structures made up of membrane that appear in electron photomicrographs as vesicles and tubules. These structures form the **sarcotubular system,** which is made up of a **T system** and a **sarcoplasmic reticulum.** The T system of transverse tubules, which is continuous with the membrane of the muscle fiber, forms a grid perforated by the individual muscle fibrils (Fig 3–1). The space between the 2 layers of the T system is an extension of the extracellular space. The sarcoplasmic reticulum forms an irregular curtain around each of the fibrils between its contacts with the T system, which in mammalian skeletal muscle is at the junction of the A and I bands. At these junctions, the arrangement of the central T system with sarcoplasmic reticulum on either side has led to the use of the term **triads** to describe the system. The function of the T system is the rapid transmission of the action potential from the cell membrane to all the fibrils in the muscle. The sarcoplasmic reticulum is concerned with Ca^{2+} movement and muscle metabolism (see below).

ELECTRICAL PHENOMENA & IONIC FLUXES

Electrical Characteristics of Skeletal Muscle

The electrical events in skeletal muscle and the ionic fluxes underlying them are similar to those in nerve, although there are quantitative differences in timing and magnitude. The resting membrane potential of skeletal muscle is about −90 mV. The action potential lasts 2–4 ms and is conducted along the muscle fiber at about 5 m/s. The absolute refractory period is 1–3 ms long and the after-polarizations, with their related changes in threshold to electrical stimulation, are relatively prolonged. The chronaxie of skeletal muscle is generally somewhat longer than that of nerve. The initiation of impulses at the myoneural junction is discussed in Chapter 4.

Although the electrical properties of the individual fibers in a muscle do not differ sufficiently to produce anything resembling a compound action potential, there are slight differences in the thresholds of the various fibers. Furthermore, in any stimulation experiment, some fibers are farther from the stimulating electrodes than others. Therefore, the size of the action potential recorded from a whole muscle preparation is proportionate to the intensity of the stimulating current between threshold and maximal current intensities.

Table 3–1. Steady-state distribution of ions in the intracellular and extracellular compartments of mammalian skeletal muscle, and the equilibrium potentials for these ions.* A^- represents organic anions. The value for intracellular Cl^- is calculated from the membrane potential, using the Nernst equation.

Ion	Concentration, mmol/L		Equilibrium Potential (mV)
	Intracellular Fluid	Extracellular Fluid	
Na^+	12	145	+65
K^+	155	4	−95
H^+	13×10^{-5}	3.8×10^{-5}	−32
Cl^-	3.8	120	−90
HCO_3^-	8	27	−32
A^-	155	0	...
Membrane Potential = −90 mV			

*Data from Ruch TC, Patton HD (editors): *Physiology and Biophysics*, 19th ed. Saunders, 1965.

Ion Distribution & Fluxes

The distribution of ions across the muscle fiber membrane is similar to that across the nerve cell membrane. The values for the various ions and their equilibrium potentials are shown in Table 3–1. As in nerve, depolarization is a manifestation of Na^+ influx, and repolarization is a manifestation of K^+ efflux (as described in Chapter 2 for nerve).

CONTRACTILE RESPONSES

It is important to distinguish between the electrical and mechanical events in muscle. Although one response does not normally occur without the other, their physiologic basis and characteristics are different. Muscle fiber membrane depolarization normally starts at the motor end-plate, the specialized structure under the motor nerve ending (see Chapter 4); the action potential is transmitted along the muscle fiber and initiates the contractile response.

The Muscle Twitch

A single action potential causes a brief contraction followed by relaxation. This response is called a **muscle twitch.** In Fig 3–4, the action potential and the twitch are plotted on the same time scale. The twitch starts about 2 ms after the start of depolarization of the membrane, before repolarization is complete. The duration of the twitch varies with the type of muscle being tested. "Fast" muscle fibers, primarily those concerned with fine, rapid, precise movement, have twitch durations as short as 7.5 ms. "Slow" muscle fibers, principally those involved in strong, gross, sustained movements, have twitch durations up to 100 ms.

Molecular Basis of Contraction

The process by which the shortening of the contractile elements in muscle is brought about is a sliding of the thin filaments over the thick filaments. The width of the A bands is constant, whereas the Z lines move closer together when the muscle contracts and farther apart when it is stretched (Fig 3–5). As the muscle shortens, the thin filaments from the opposite ends of the sarcomere approach each other; when the shortening is marked, these filaments apparently overlap.

The sliding during muscle contraction is produced by breaking and re-forming of the cross-linkages between actin and myosin. The heads of the myosin molecules link to actin at an angle, produce movement of myosin on actin by swiveling, and then disconnect and reconnect at the next linking site, repeating the process in serial fashion (Fig 3–6). Each single cycle of attaching, swiveling, and detaching shortens the muscle 1%.

The immediate source of energy for muscle contraction is ATP (Fig 1–22). Hydrolysis of the bonds between the phosphate residues of this compound is associated with the release of a large amount of energy, and the bonds are therefore referred to as high-energy phosphate bonds. In muscle, the hydrolysis of ATP to adenosine diphosphate (ADP) is catalyzed by the contractile protein myosin; this **adenosine triphosphatase (ATPase)** activity is found in the heads of the myosin molecules, where they are in contact with actin.

The process by which depolarization of the muscle fiber initiates contraction is called **excitation-contraction coupling.** The action potential is transmitted to all the fibrils in the fiber via the T system. It triggers the release of Ca^{2+} from the **terminal cisterns,** the lateral sacs of the sarcoplasmic reticulum next to the T system (Fig 3–5). The Ca^{2+} initiates contraction.

Ca^{2+} initiates contraction by binding to troponin C. In resting muscle, troponin I is tightly bound to

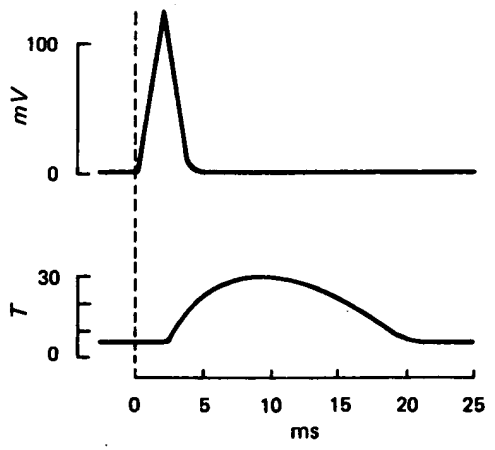


Figure 3–4. The electrical and mechanical responses of a mammalian skeletal muscle fiber to a single maximal stimulus. The electrical response (mV potential change) and the mechanical response (T, tension in arbitrary units) are plotted on the same abscissa (time).

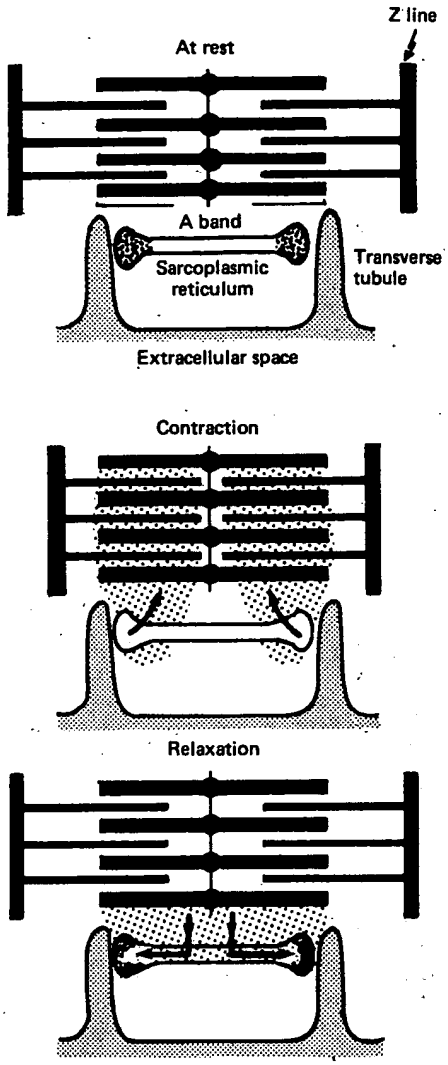
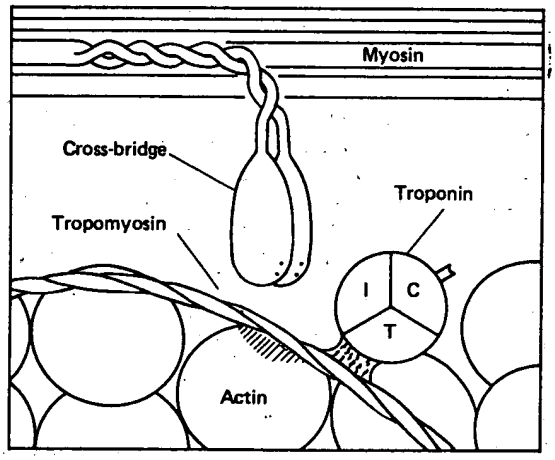


Figure 3–5. Muscle contraction. Calcium ions (represented by black dots) are normally stored in the cisterns of the sarcoplasmic reticulum. The action potential spreads via the transverse tubules and releases Ca^{2+}. The thin filaments (thin lines) slide on the thick filaments, and the Z lines move closer together. Ca^{2+} is then pumped into the sarcoplasmic reticulum, and the muscle relaxes. (Modified from Layzer RB, Rowland LP: Cramps. *N Engl J Med* 1971;285:31.)

actin, and tropomyosin covers the sites where myosin heads bind to actin. Thus, the troponin-tropomyosin complex constitutes a "relaxing protein" that inhibits the interaction between actin and myosin. When the Ca^{2+} released by the action potential binds to troponin C, the binding of troponin I to actin is presumably weakened, and this permits the tropomyosin to move laterally (Fig 3–6). This movement uncovers binding sites for the myosin heads, so that ATP is split and contraction occurs. Seven myosin binding sites are uncovered for each molecule of troponin that binds a calcium ion.

Shortly after releasing Ca^{2+}, the sarcoplasmic reticulum begins to reaccumulate Ca^{2+}. The Ca^{2+} is actively pumped into longitudinal portions of the reticulum and diffuses from there to the cisterns, where it is stored (Fig 3–5). Once the Ca^{2+} concentration outside of the reticulum has been lowered sufficiently, chemical interaction between myosin and actin ceases and the muscle relaxes. If the active transport of Ca^{2+} is inhibited, relaxation does not occur even though there are no more action potentials; the resulting sustained contraction is called a **contracture.** It should be noted that ATP provides the energy for the active transport of Ca^{2+} into the sarcoplasmic reticulum. Thus, both contraction and relaxation of muscle require ATP.

The events involved in muscle contraction and relaxation are summarized in Table 3–2.



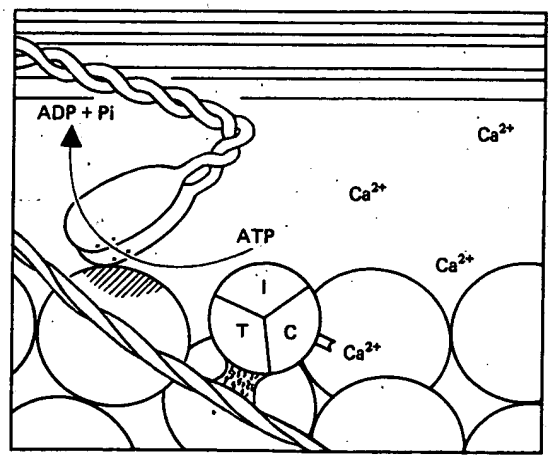


Figure 3–6. Initiation of muscle contraction by Ca^{2+}. The cross-bridges (heads of myosin molecules) attach to binding sites on actin (striped areas) and swivel when tropomyosin is displaced laterally by binding of Ca^{2+} to troponin C. (Modified from Katz AM: Congestive heart failure. *N Engl J Med* 1975;293:1184.)

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